FILE 'HOME' ENTERED AT 11:20:25 ON 25 JAN 2007

=> **file registry**

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 0.21 | 0.21 |

FILE 'REGISTRY' ENTERED AT 11:20:33 ON 25 JAN 2007


Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 24 JAN 2007 HIGHEST RN 918400-64-3
DICTIONARY FILE UPDATES: 24 JAN 2007 HIGHEST RN 918400-64-3

New CAS Information Use Policies, enter HELP USAGETERMS for details.

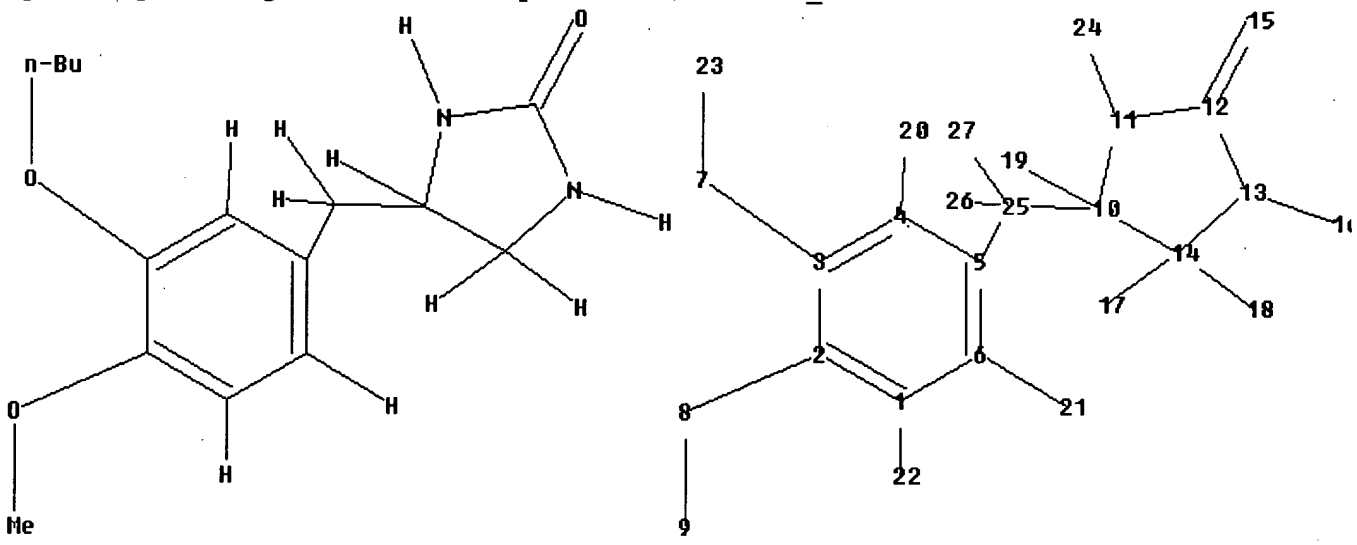
TSCA INFORMATION NOW CURRENT THROUGH June 30, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading C:\Program Files\Stnexp\Queries\10060759_RO201724.str



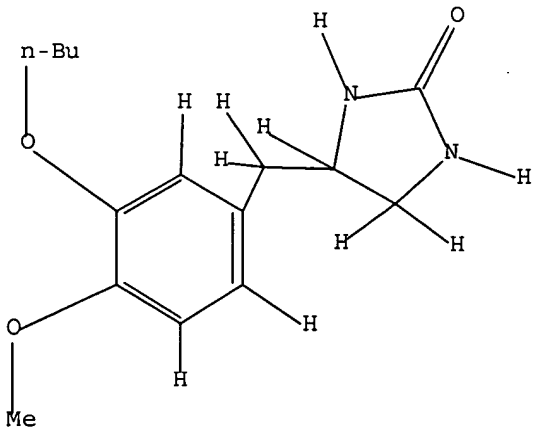

chain nodes :
7 8 9 15 16 17 18 19 20 21 22 23 24 25 26 27
ring nodes :
1 2 3 4 5 6 10 11 12 13 14
chain bonds :
1-22 2-8 3-7 4-20 5-25 6-21 7-23 8-9 10-19 10-25 11-24 12-15 13-16 14-

17
14-18  25-26  25-27
ring bonds :
1-2  1-6  2-3  3-4  4-5  5-6  10-11  10-14  11-12  12-13  13-14
exact/norm bonds :
2-8  3-7  10-11  10-14  11-12  12-13  12-15  13-14
exact bonds :
1-22  4-20  5-25  6-21  7-23  8-9  10-19  10-25  11-24  13-16  14-17  14-18  25-26
25-27
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6

Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:CLASS  8:CLASS  9:CLASS  10:Atom
11:Atom  12:Atom  13:Atom  14:Atom  15:CLASS  16:CLASS  17:CLASS  18:CLASS
19:CLASS  20:CLASS
21:CLASS  22:CLASS  23:CLASS  24:CLASS  25:CLASS  26:CLASS  27:CLASS

L1  STRUCTURE UPLOADED

=> **d l1**
L1 HAS NO ANSWERS
L1  STR




Structure attributes must be viewed using STN Express query preparation.

=> **s l1 exa**
SAMPLE SEARCH INITIATED 11:20:52 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -  2 TO ITERATE

100.0% PROCESSED  2 ITERATIONS  0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH  **COMPLETE**
PROJECTED ITERATIONS:  2 TO  124

PROJECTED ANSWERS: 0 TO 0

L2 0 SEA EXA SAM L1

=> **s l1**
SAMPLE SEARCH INITIATED 11:21:16 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 20 TO ITERATE

100.0% PROCESSED 20 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 132 TO 668
PROJECTED ANSWERS: 0 TO 0

L3 0 SEA SSS SAM L1

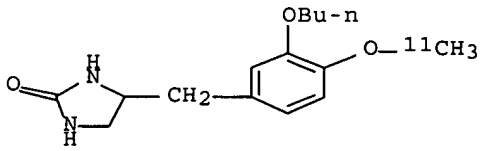
=> **s l1 full**
FULL SEARCH INITIATED 11:21:20 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 306 TO ITERATE

100.0% PROCESSED 306 ITERATIONS 4 ANSWERS
SEARCH TIME: 00.00.01

L4 4 SEA SSS FUL L1

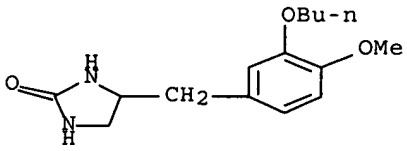
=> **d scan**

L4 4 ANSWERS REGISTRY COPYRIGHT 2007 ACS on STN
IN 2-Imidazolidinone, 4-[[3-butoxy-4-(methoxy-11C)phenyl]methyl]- (9CI)
MF C15 H22 N2 O3




HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L4 4 ANSWERS REGISTRY COPYRIGHT 2007 ACS on STN
IN 2-Imidazolidinone, 4-[(3-butoxy-4-methoxyphenyl)methyl]- (9CI)
MF C15 H22 N2 O3

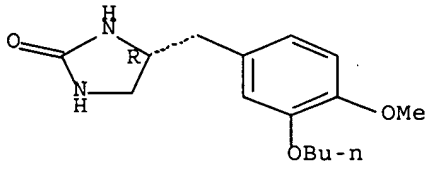


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L4 4 ANSWERS REGISTRY COPYRIGHT 2007 ACS on STN
IN 2-Imidazolidinone, 4-[(3-butoxy-4-methoxyphenyl)methyl]-, (R)- (9CI)
MF C15 H22 N2 O3

Absolute stereochemistry.

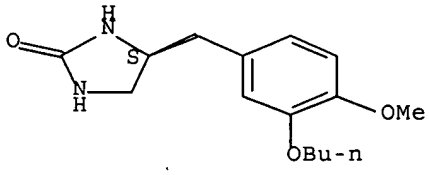



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L4 4 ANSWERS REGISTRY COPYRIGHT 2007 ACS on STN
IN 2-Imidazolidinone, 4-[(3-butoxy-4-methoxyphenyl)methyl]-, (S)- (9CI)
MF C15 H22 N2 O3

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

ALL ANSWERS HAVE BEEN SCANNED

=> **d his**

(FILE 'HOME' ENTERED AT 11:20:25 ON 25 JAN 2007)

FILE 'REGISTRY' ENTERED AT 11:20:33 ON 25 JAN 2007

```
L1              STRUCTURE UPLOADED
L2            0 S L1 EXA
L3            0 S L1
L4            4 S L1 FULL

=> file medline, caplus, wpids, uspatfull
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   172.55     172.76

FILE 'MEDLINE' ENTERED AT 11:21:56 ON 25 JAN 2007

FILE 'CAPLUS' ENTERED AT 11:21:56 ON 25 JAN 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'WPIDS' ENTERED AT 11:21:56 ON 25 JAN 2007
COPYRIGHT (C) 2007 THE THOMSON CORPORATION

FILE 'USPATFULL' ENTERED AT 11:21:56 ON 25 JAN 2007
CA INDEXING COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

=> s l4
SAMPLE SEARCH INITIATED 11:22:03 FILE 'WPIDS'
SAMPLE SCREEN SEARCH COMPLETED -        0 TO ITERATE

100.0% PROCESSED        0 ITERATIONS                              0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            0 TO        0
PROJECTED ANSWERS:               0 TO        0

L5          866 L4

=> s l5 not py>1998
L6          629 L5 NOT PY>1998

=> s l6 and (CLL or "chronic lymphocytic leukemia")
L7            0 L6 AND (CLL OR "CHRONIC LYMPHOCYTIC LEUKEMIA")

=> s l6 and leukemia
L8            6 L6 AND LEUKEMIA

=> d l8 1-6 ibib, abs, hitstr

L8   ANSWER 1 OF 6     MEDLINE on STN
ACCESSION NUMBER:    97318782     MEDLINE  Full-text
DOCUMENT NUMBER:     PubMed ID: 9175719
TITLE:               Dissociation between phosphodiesterase inhibition and
                     antiproliferative effects of phosphodiesterase inhibitors
                     on the Dami cell line.
AUTHOR:              Zurbonsen K; Michel A; Vittet D; Bonnet P A; Chevillard C
CORPORATE SOURCE:    INSERM U.300, Montpellier, France.
SOURCE:              Biochemical pharmacology, (1997 Apr 25) Vol. 53, No. 8, pp.
                     1141-7.
                     Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY:        ENGLAND: United Kingdom
```

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 30 Jun 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 17 Jun 1997

AB Phosphodiesterase (PDE) inhibitors were shown to inhibit proliferation of various cell types. The present investigation was designed to study the activity of selective PDE inhibitors (8-MeoMIX, milrinone, trequinsin, rolipram, RO-201724, zaprinast, and MY-5445) on the proliferation of the Dami cell line in relation to their effects on cAMP levels and PDE isoenzymes isolated from Dami cells. All compounds, except 8-MeoMIX, elicited antiproliferative effects. Trequinsin, RO-201724, and MY-5445 (100 microM) were found to inhibit cell growth up to 60%, 83%, and 85%, respectively; milrinone, rolipram and zaprinast elicited only weak effects (19-21% at 100 microM). Their growth-inhibitory effects could not be related to their effects on cAMP levels. In addition, although PDE type III and IV inhibitors potentiated cAMP formation due to adenylycyclase activation, no potentiation could be observed when considering their antiproliferative effect. Separation and characterization of PDE of Dami cells revealed the existence of types III, IV, and V isoenzymes. The PDE inhibition found for the PDE inhibitors could not explain their antiproliferative effects. The lack of correlation with cAMP concentrations or PDE inhibition and the high concentrations needed to elicit antiproliferative effects suggest the implication of other parameters, such as cytotoxicity or lipophilicity, or other targets in addition to PDE for the PDE inhibitors tested. Lipophilicity did not seem to be of importance in antiproliferative effects. In contrast, cytotoxic effects, in particular those of trequinsin and MY-5445, could partially explain their negative action on cell growth.

L8 ANSWER 2 OF 6 MEDLINE on STN
ACCESSION NUMBER: 97008163 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8855339
TITLE: Inhibition of calmodulin-dependent phosphodiesterase induces apoptosis in human leukemic cells.
AUTHOR: Jiang X; Li J; Paskind M; Epstein P M
CORPORATE SOURCE: Department of Pharmacology, University of Connecticut Health Center, Farmington 06030, USA.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1996 Oct 1) Vol. 93, No. 20, pp. 11236-41.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U56976
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19 Dec 1996
Last Updated on STN: 3 Mar 2000
Entered Medline: 25 Nov 1996

AB Cytosolic extracts from a human lymphoblastoid B-cell line, RPMI-8392, established from a patient with acute lymphocytic leukemia, contain two major forms of cyclic nucleotide phosphodiesterase (PDE): Ca2+-calmodulin dependent PDE (PDE1) and cAMP-specific PDE (PDE4). In contrast, normal quiescent human peripheral blood lymphocytes (HPBL) are devoid of PDE1 activity [Epstein, P. M., Moraski, S., Jr., and Hachisu, R. (1987) Biochem. J. 243, 533-539]. Using reverse transcription- polymerase chain reaction (RT-PCR), we show that

the mRNA encoding the 63-kDa form of PDE1 (PDE1B1) is expressed in RPMI-8392 cells, but not in normal, resting HPBL. This mRNA is, however, induced in HPBL following mitogenic stimulation by phytohemagglutinin (PHA). Also using RT-PCR, the full open reading frame for human PDE1B1 cDNA was cloned from RPMI-8392 cells and it encodes a protein of 536 amino acids with 96% identity to bovine, rat, and mouse species. RT-PCR also identifies the presence of PDE1B1 in other human lymphoblastoid and leukemic cell lines of B- (RPMI-1788, Daudi) and T-(MOLT-4, NA, Jurkat) cell origin. Inhibition of PDE1 or PDE4 activity by selective inhibitors induced RPMI-8392 cells, as well as the other cell lines, to undergo apoptosis. Culture of RPMI-8392 cells with an 18-bp phosphorothioate antisense oligodeoxynucleotide, targeted against the translation initiation region of the RPMI-8392 mRNA, led to a specific reduction in the amount of PDE1B1 mRNA after 1 day, and its disappearance after 2 days, and induced apoptosis in these cells in a sequence specific manner. This suggests that PDEs, particularly PDE1B1, because its expression is selective, may be useful targets for inducing the death of leukemic cells.

L8 ANSWER 3 OF 6 MEDLINE on STN
ACCESSION NUMBER: 95061906 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 7971738
TITLE: Effects of cAMP and cGMP elevating agents on HL-60 cell differentiation.
AUTHOR: Bang B E; Ericsen C; Aarbakke J
CORPORATE SOURCE: Department of Pharmacology, University of Tromso, Norway.
SOURCE: Pharmacology & toxicology, (1994 Aug) Vol. 75, No. 2, pp. 108-12.
Journal code: 8702180. ISSN: 0901-9928.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 10 Jan 1995
Last Updated on STN: 10 Jan 1995
Entered Medline: 6 Dec 1994

AB Previous studies have demonstrated low percentage of HL-60 cell differentiation with theophylline. The present study demonstrate that millimolar concentrations of the non-selective phosphodiesterase inhibitors theophylline, caffeine and isobutyl-methylxanthine all inhibit growth, induce substantial differentiation and elevation of both cAMP and cGMP in HL-60 cells. Selective inhibition of cAMP hydrolysis by Ro20-1724 was without effect. The guanylate cyclase stimulator sodium nitroprusside, which increased cGMP only poorly and also increased cAMP, produced growth inhibition but no differentiation. We put forward the hypothesis that elevation of both cAMP and cGMP above a critical level is necessary for significant cyclic nucleotide induced HL-60 cell differentiation.

L8 ANSWER 4 OF 6 MEDLINE on STN
ACCESSION NUMBER: 90137009 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 2559336
TITLE: Histamine inhibits activation of human neutrophils and HL-60 leukemic cells via H2-receptors.
AUTHOR: Burde R; Seifert R; Buschauer A; Schultz G
CORPORATE SOURCE: Institut fur Pharmakologie, Freie Universitat Berlin.
SOURCE: Naunyn-Schmiedeberg's archives of pharmacology, (1989 Dec) Vol. 340, No. 6, pp. 671-8.
Journal code: 0326264. ISSN: 0028-1298.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199003
ENTRY DATE: Entered STN: 28 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 12 Mar 1990

AB The effects of prostaglandin E1 (PGE1) and histamine on activation of superoxide (O2-) formation, exocytosis of beta-glucuronidase and aggregation in human neutrophils and HL-60 leukemic cells were studied. PGE1, histamine and impromidine, a potent H2-agonist, inhibited O2- formation in neutrophils induced by the chemotactic peptide, N-formyl-L-methionyl-L-leucyl-L-phenylalanine (fMet-Leu-Phe) with IC50 values of 0.5 microM, 8 microM and 2 microM, respectively. The full H1-agonist and weak partial H2-agonist, betahistine, was much less potent and effective than histamine. Dibutyryl cyclic AMP and forskolin mimicked the effects of histamine and PGE1 on O2- formation. The H2-antagonist, famotidine, competitively reversed histamine-induced inhibition of O2- formation with a pA2 value of 7.5. Histamine inhibited O2- formation when added prior to or after fMet-Leu-Phe. fMet-Leu-Phe-induced aggregation and release of beta-glucuronidase in neutrophils were less sensitive to inhibition by PGE1, histamine, dibutyryl cyclic AMP and forskolin than O2- formation. The inhibitor of cyclic AMP-specific phosphodiesterase, rac-4-(3-butoxy-4-methoxybenzyl)-2-imidazolidinone (Ro 20-1724), additively enhanced the inhibitory effects of histamine and PGE1 on the above cell functions. In HL-60 cells differentiated by dimethyl sulfoxide or dibutyryl cyclic AMP, histamine, impromidine and PGE1 but not betahistine inhibited fMet-Leu-Phe-induced O2- formation as well. Our data suggest that histamine inhibits activation of neutrophils and HL-60 cells via H2-receptors through activation of adenylyl cyclase and increased formation of cyclic AMP.(ABSTRACT TRUNCATED AT 250 WORDS)

L8 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:465856 CAPLUS Full-text
DOCUMENT NUMBER: 129:242969
TITLE: Hydroxyl radical-mediated commitment of HL-60 cells to differentiation: modulation of differentiation process by phosphodiesterase inhibitors
AUTHOR(S): Cho, Young Jin; Ahn, Woong Shick; Cha, Seok Ho; Lee, Kweon-Haeng; Kim, Won Il; Chung, Myung Hee
CORPORATE SOURCE: Department of Pharmacology, Catholic University Medical College, Seoul, 137-701, S. Korea
SOURCE: Korean Journal of Physiology & Pharmacology (1998), 2(3), 369-376
CODEN: KJPPFS; ISSN: 1226-4512
PUBLISHER: Korean Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

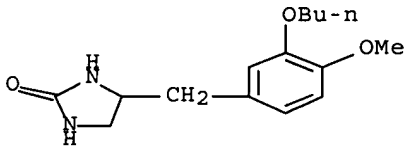
AB This report shows that hydroxyl radical, generated by a Fenton reaction involving ADP/Fe2+ complex (5-15 μM) and H2O2 (2 μM), induced differentiation of HL-60 cells in a dose- and time-dependent manner. This is evidenced by the increases in 12-O-tetradecanoylphorbol 13-acetate- and fMLP-stimulated superoxide production capability. The cells exposed to hydroxyl radical for defined periods (24.apprx.96 h) continued to differentiate even after the hydroxyl radical generating system had been removed. The differentiated cells displayed fMLP-stimulated calcium mobilization and increased expression of myeloid-specific antigen CD11b and CD14. The extent of the differentiation was markedly reduced by desferrioxamine (100 μM), dimethylthiourea (5 mM), N,N'-diphenyl-1,4- phenylenediamine (2 μM), and N-acetyl-L-cysteine (5 mM).

The induction of differentiation by hydroxyl radical was enhanced by 3-isobutyl-1-methylxanthine (200 μM) and Ro-20-1724 (8 μM), and inhibited by dipyridamole (2 μM). These results suggest that hydroxyl radicals may induce commitment of HL-60 cells to differentiate into more mature cells of myelomonocytic lineage through specific signal-transduction pathway that is modulated by phosphodiesterase inhibitors.

IT 29925-17-5, Ro-20-1724
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(hydroxyl radical-mediated commitment of HL-60 cells to differentiation and modulation of differentiation process by phosphodiesterase inhibitors)

RN 29925-17-5 CAPLUS

CN 2-Imidazolidinone, 4-[(3-butoxy-4-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:414523 CAPLUS Full-text
DOCUMENT NUMBER: 129:130969

TITLE: Cyclic AMP-specific phosphodiesterase inhibitor rolipram and RO-20-1724 promoted apoptosis in HL60 promyelocytic leukemic cells via cyclic AMP-independent mechanism

AUTHOR(S): Zhu, Wen-Hui; Majluf-Cruz, Abraham; Omburo, George A.
CORPORATE SOURCE: The Sol Sherry Thrombosis Research Center, Temple University School of Medicine, Philadelphia, PA, 19140, USA

SOURCE: Life Sciences (1998), 63(4), 265-274
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

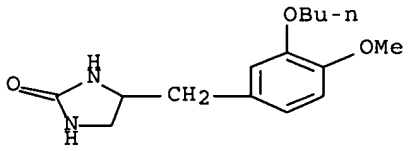
AB Phosphodiesterases (PDEs) are responsible for the hydrolysis of cAMP and cGMP which act as intracellular second messengers in a variety of cellular functions. In this paper we report that PDE3 and PDE4 were two dominant classes of PDEs expressed in HL60 cells. The influence of specific PDE inhibitors on apoptosis in HL60 cells was studied. The nonspecific inhibitor IBMX and PDE3-specific inhibitors (milrinone and trequinsin) did not promote apoptosis. They inhibited apoptosis induced by paclitaxel or thapsigargin. However, PDE4-specific inhibitors (rolipram and RO-20-1724) promoted apoptosis within 5 h. In HL60 cells, other cAMP-eliciting reagents (8-bromo-cAMP, Sp-cAMP and forskolin) also inhibited apoptosis, while cell-permeable cGMP analogs did not affect apoptosis. Therefore, IBMX and PDE3-specific inhibitors may prevent HL60 cells from apoptosis by increasing intracellular cAMP. However, apoptosis induced by PDE4-specific inhibitors is not likely

due to increased cAMP level. These results suggest that rolipram and RO-20-1724 promoted apoptosis in HL60 cells through cAMP-independent mechanism.

IT 29925-17-5, RO-20-1724
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rolipram and RO-201724 promote apoptosis in promyelocytic leukemia via cAMP-independent mechanism)

RN 29925-17-5 CAPLUS

CN 2-Imidazolidinone, 4-[(3-butoxy-4-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 11:20:25 ON 25 JAN 2007)

FILE 'REGISTRY' ENTERED AT 11:20:33 ON 25 JAN 2007
L1 STRUCTURE UPLOADED
L2 0 S L1 EXA
L3 0 S L1
L4 4 S L1 FULL

FILE 'MEDLINE, CAPLUS, WPIDS, USPATFULL' ENTERED AT 11:21:56 ON 25 JAN 2007
L5 866 S L4
L6 629 S L5 NOT PY>1998
L7 0 S L6 AND (CLL OR "CHRONIC LYMPHOCYTIC LEUKEMIA")
L8 6 S L6 AND LEUKEMIA

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 33.01 | 205.77 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE | TOTAL |
|---|---|---|

| | ENTRY | SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -1.56 | -1.56 |

STN INTERNATIONAL LOGOFF AT 11:24:27 ON 25 JAN 2007

FILE 'HOME' ENTERED AT 10:42:14 ON 25 JAN 2007

=> **file registry**

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 0.21 | 0.21 |

FILE 'REGISTRY' ENTERED AT 10:42:28 ON 25 JAN 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.


Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 24 JAN 2007 HIGHEST RN 918400-64-3
DICTIONARY FILE UPDATES: 24 JAN 2007 HIGHEST RN 918400-64-3

New CAS Information Use Policies, enter HELP USAGETERMS for details.

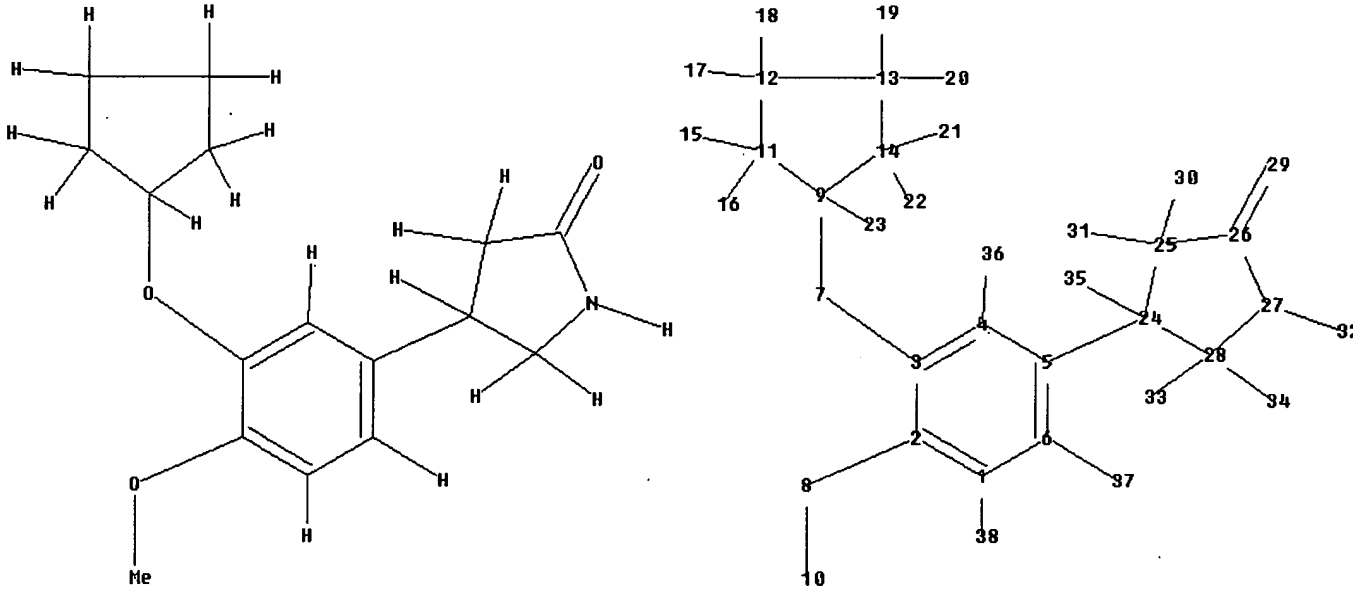
TSCA INFORMATION NOW CURRENT THROUGH June 30, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading C:\Program Files\Stnexp\Queries\10060759_rolipram.str



chain nodes :
7 8 10 15 16 17 18 19 20 21 22 23 29 30 31 32 33 34 35 36 37 38
ring nodes :

1 2 3 4 5 6 9 11 12 13 14 24 25 26 27 28
chain bonds :
1-38 2-8 3-7 4-36 5-24 6-37 7-9 8-10 9-23 11-15 11-16 12-17 12-18 13-19
13-20 14-21 14-22 24-35 25-30 25-31 26-29 27-32 28-33 28-34
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 9-11 9-14 11-12 12-13 13-14 24-25 24-28 25-26 26-27 27-28
exact/norm bonds :
2-8 3-7 7-9 9-11 9-14 11-12 12-13 13-14 24-25 24-28 25-26 26-27 26-29 27-28
exact bonds :
1-38 4-36 5-24 6-37 8-10 9-23 11-15 11-16 12-17 12-18 13-19 13-20 14-21 14-22 24-35 25-30 25-31 27-32 28-33 28-34
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6

Match level :
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21:CLASS 22:CLASS 23:CLASS 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:CLASS 30:CLASS 31:CLASS
32:CLASS 33:CLASS 34:CLASS 35:CLASS 36:CLASS 37:CLASS 38:CLASS

L1 STRUCTURE UPLOADED

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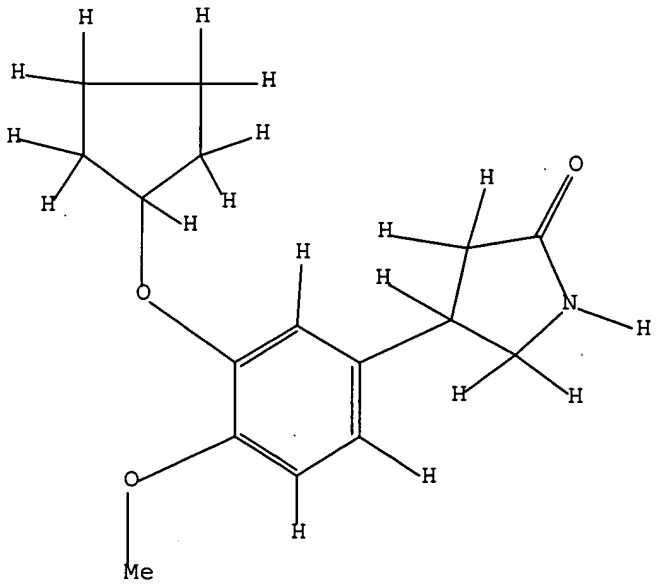


Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED - 2 TO ITERATE

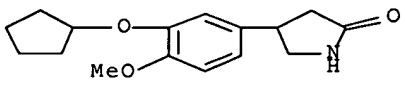
100.0% PROCESSED 2 ITERATIONS 1 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 2 TO 124
PROJECTED ANSWERS: 1 TO 80

L2 1 SEA EXA SAM L1

=> **d l2**

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN
RN 61413-54-5 REGISTRY
ED Entered STN: 16 Nov 1984
CN 2-Pyrrolidinone, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (±)-Rolipram
CN (R,S)-Rolipram
CN 4-[3-(Cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone
CN Rolipram
CN SB 95952
CN ZK 62711
DR 85416-74-6
MF C16 H21 N O3
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, PROUSDDR, RTECS*, SCISEARCH, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1015 REFERENCES IN FILE CA (1907 TO DATE)
19 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1022 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> **file medline, caplus, wpids, uspatfull**
COST IN U.S. DOLLARS SINCE FILE TOTAL

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                                                        ENTRY    SESSION
FULL ESTIMATED COST                                      2.40       2.61

FILE 'MEDLINE' ENTERED AT 10:43:08 ON 25 JAN 2007

FILE 'CAPLUS' ENTERED AT 10:43:08 ON 25 JAN 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'WPIDS' ENTERED AT 10:43:08 ON 25 JAN 2007
COPYRIGHT (C) 2007 THE THOMSON CORPORATION

FILE 'USPATFULL' ENTERED AT 10:43:08 ON 25 JAN 2007
CA INDEXING COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

=> s l2
SAMPLE SEARCH INITIATED 10:43:13 FILE 'WPIDS'
SAMPLE SCREEN SEARCH COMPLETED -       20 TO ITERATE

100.0% PROCESSED       20 ITERATIONS                              0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:           66 TO      334
PROJECTED ANSWERS:               0 TO        0

L3        2155 L2

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L4         995 L3 NOT PY>1998

=> s l4 and leukemia
L5           7 L4 AND LEUKEMIA

=> s l4 and CLL or "chronic lymphocytic leukemia"
L6       16789 L4 AND CLL OR "CHRONIC LYMPHOCYTIC LEUKEMIA"

=> s l4 and (CLL or "chronic lymphocytic leukemia")
L7           2 L4 AND (CLL OR "CHRONIC LYMPHOCYTIC LEUKEMIA")

=> d l7 1-2 ibib, abs, hitstr

L7   ANSWER 1 OF 2     MEDLINE on STN
ACCESSION NUMBER:   1998421394     MEDLINE  Full-text
DOCUMENT NUMBER:    PubMed ID: 9746789
TITLE:              Type 4 cyclic adenosine monophosphate phosphodiesterase as
                    a therapeutic target in chronic
                    lymphocytic leukemia.
AUTHOR:             Kim D H; Lerner A
CORPORATE SOURCE:   Department of Medicine, Section of Hematology and Oncology,
                    Boston Medical Center, Boston, MA 02118, USA.
SOURCE:             Blood, (1998 Oct 1) Vol. 92, No. 7, pp. 2484-94.
                    Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:        199810
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ENTRY DATE: Entered STN: 29 Oct 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 19 Oct 1998

AB Theophylline, a drug known to inhibit several classes of adenosine 3'5' cyclic monophosphate (cAMP) phosphodiesterases (PDEs), induces apoptosis in chronic lymphocytic leukemia (CLL ) cells. Because the PDE target for theophylline in CLL remains unknown, we examined the ability of isoform-specific PDE inhibitors to increase cAMP levels and induce apoptosis in primary CLL cells. Reverse transcriptase-polymerase chain reaction of purified CLL cDNA amplified transcripts for PDE1B, 4A and 4B. The type 4 PDE inhibitor rolipram but not the type 1 inhibitor vinpocetine increased CLL cAMP levels. Rolipram-inhibitable (type 4) but not calcium-calmodulin augmented (type 1) PDE enzyme activity was detected in CLL samples. In samples from 13 of 14 CLL patients, rolipram induced apoptosis in a dose-dependent fashion over a 48-hour period. Interleukin-2 (IL-2)-cultured whole mononuclear cells (WMC) and anti-Ig stimulated CD19(+) B cells were resistant to the induction of apoptosis by rolipram while unstimulated CD19(+) B cells, which had a high basal apoptotic rate, were more sensitive. Rolipram stimulated elevations in cAMP levels in all four of these cell populations, suggesting that they differed in sensitivity to cAMP-induced apoptosis. Consistent with this hypothesis, incubation with the cell permeable cAMP analog dibutyryl-cAMP induced apoptosis in CLL cells and unstimulated B cells but not in IL-2-cultured WMC or anti-Ig stimulated B cells. These data identify PDE4 as a family of enzymes whose inhibition induces apoptosis in CLL cells.

L7 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:646421 CAPLUS Full-text
DOCUMENT NUMBER: 130:261
TITLE: Type 4 cyclic adenosine monophosphate phosphodiesterase as a therapeutic target in chronic lymphocytic leukemia
AUTHOR(S): Kim, Doo Ho; Lerner, Adam
CORPORATE SOURCE: Department of Medicine, Section of Hematology and Oncology, Boston Medical Center, Boston, MA, 02118, USA
SOURCE: Blood (1998), 92(7), 2484-2494
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

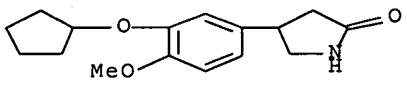
AB Theophylline, a drug known to inhibit several classes of adenosine 3'5' cyclic monophosphate (cAMP) phosphodiesterases (PDEs), induces apoptosis in chronic lymphocytic leukemia (CLL ) cells. Because the PDE target for theophylline in CLL remains unknown, the authors examined the ability of isoform-specific PDE inhibitors to increase cAMP levels and induce apoptosis in primary CLL cells. Reverse transcriptase-polymerase chain reaction of purified CLL cDNA amplified transcripts for PDE1B, 4A and 4B. The type 4 PDe inhibitor rolipram but not the type 1 inhibitor vinpocetine increased CLL cAMP levels. Rolipram-inhibitable (type 4) but not calcium-calmodulin augmented (type 1) PDE enzyme activity was detected in CLL samples. In samples from 13 of 14 CLL patients, rolipram induced apoptosis in a dose-dependent fashion over a 48-h period. Interleukin-2 (IL-2)-cultured whole mononuclear cells (WMC) and anti-Ig stimulated CD19+ B cells were resistant to the induction of apoptosis by rolipram while unstimulated CD19+ B cells, which had a high basal apoptotic rate, were more sensitive. Rolipram stimulated elevations in cAMP levels in all four of these cell populations, suggesting that they differed in sensitivity to cAMP-induced apoptosis. Consistent with this hypothesis, incubation with the cell permeable cAMP analog dibutyryl-cAMP induced apoptosis in CLL cells and unstimulated B cells but not in IL-2-cultured WMC

or anti-Ig stimulated B cells. These data identify PDE4 as a family of enzymes whose inhibition induces apoptosis in CLL cells.

IT 61413-54-5, Rolipram
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(4 cyclic adenosine monophosphate phosphodiesterase as a therapeutic target in chronic lymphocytic leukemia)

RN 61413-54-5 CAPLUS

CN 2-Pyrrolidinone, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]- (9CI) (CA INDEX NAME)




REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> **FIL STNGUIDE**

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 32.52 | 35.13 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -0.78 | -0.78 |

FILE 'STNGUIDE' ENTERED AT 10:44:52 ON 25 JAN 2007


FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jan 19, 2007 (20070119/UP).

=> **d 15 1-7 ibib, abs, hitstr**
YOU HAVE REQUESTED DATA FROM FILE 'MEDLINE, CAPLUS' - CONTINUE? (Y)/N:y

L5 ANSWER 1 OF 7 MEDLINE on STN
ACCESSION NUMBER: 1998421394 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9746789
TITLE: Type 4 cyclic adenosine monophosphate phosphodiesterase as a therapeutic target in chronic lymphocytic leukemia.
AUTHOR: Kim D H; Lerner A
CORPORATE SOURCE: Department of Medicine, Section of Hematology and Oncology, Boston Medical Center, Boston, MA 02118, USA.
SOURCE: Blood, (1998 Oct 1) Vol. 92, No. 7, pp. 2484-94.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 29 Oct 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 19 Oct 1998

AB Theophylline, a drug known to inhibit several classes of adenosine 3'5' cyclic monophosphate (cAMP) phosphodiesterases (PDEs), induces apoptosis in chronic lymphocytic leukemia (CLL) cells. Because the PDE target for theophylline in CLL remains unknown, we examined the ability of isoform-specific PDE inhibitors to increase cAMP levels and induce apoptosis in primary CLL cells. Reverse transcriptase-polymerase chain reaction of purified CLL cDNA amplified transcripts for PDE1B, 4A and 4B. The type 4 PDE inhibitor rolipram but not the type 1 inhibitor vinpocetine increased CLL cAMP levels. Rolipram-inhibitable (type 4) but not calcium-calmodulin augmented (type 1) PDE enzyme activity was detected in CLL samples. In samples from 13 of 14 CLL patients, rolipram induced apoptosis in a dose-dependent fashion over a 48-hour period. Interleukin-2 (IL-2)-cultured whole mononuclear cells (WMC) and anti-Ig stimulated CD19(+) B cells were resistant to the induction of apoptosis by rolipram while unstimulated CD19(+) B cells, which had a high basal apoptotic rate, were more sensitive. Rolipram stimulated elevations in cAMP levels in all four of these cell populations, suggesting that they differed in sensitivity to cAMP-induced apoptosis. Consistent with this hypothesis, incubation with the cell permeable cAMP analog dibutyryl-cAMP induced apoptosis in CLL cells and unstimulated B cells but not in IL-2-cultured WMC or anti-Ig stimulated B cells. These data identify PDE4 as a family of enzymes whose inhibition induces apoptosis in CLL cells.

L5 ANSWER 2 OF 7 MEDLINE on STN
ACCESSION NUMBER: 97318782 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9175719
TITLE: Dissociation between phosphodiesterase inhibition and antiproliferative effects of phosphodiesterase inhibitors on the Dami cell line.
AUTHOR: Zurbonsen K; Michel A; Vittet D; Bonnet P A; Chevillard C
CORPORATE SOURCE: INSERM U.300, Montpellier, France.
SOURCE: Biochemical pharmacology, (1997 Apr 25) Vol. 53, No. 8, pp. 1141-7.
Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 30 Jun 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 17 Jun 1997

AB Phosphodiesterase (PDE) inhibitors were shown to inhibit proliferation of various cell types. The present investigation was designed to study the activity of selective PDE inhibitors (8-MeoMIX, milrinone, trequinsin, rolipram, RO-201724, zaprinast, and MY-5445) on the proliferation of the Dami cell line in relation to their effects on cAMP levels and PDE isoenzymes isolated from Dami cells. All compounds, except 8-MeoMIX, elicited antiproliferative effects. Trequinsin, RO-201724, and MY-5445 (100 microM) were found to inhibit cell growth up to 60%, 83%, and 85%, respectively; milrinone, rolipram and zaprinast elicited only weak effects (19-21% at 100 microM). Their growth-inhibitory effects could not be related to their effects on cAMP levels. In addition, although PDE type III and IV inhibitors potentiated cAMP formation due to adenylycyclase activation, no potentiation could be observed when considering their antiproliferative effect. Separation

and characterization of PDE of Dami cells revealed the existence of types III, IV, and V isoenzymes. The PDE inhibition found for the PDE inhibitors could not explain their antiproliferative effects. The lack of correlation with cAMP concentrations or PDE inhibition and the high concentrations needed to elicit antiproliferative effects suggest the implication of other parameters, such as cytotoxicity or lipophilicity, or other targets in addition to PDE for the PDE inhibitors tested. Lipophilicity did not seem to be of importance in antiproliferative effects. In contrast, cytotoxic effects, in particular those of trequinsin and MY-5445, could partially explain their negative action on cell growth.

L5 ANSWER 3 OF 7 MEDLINE on STN
ACCESSION NUMBER: 97008163 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8855339
TITLE: Inhibition of calmodulin-dependent phosphodiesterase induces apoptosis in human leukemic cells.
AUTHOR: Jiang X; Li J; Paskind M; Epstein P M
CORPORATE SOURCE: Department of Pharmacology, University of Connecticut Health Center, Farmington 06030, USA.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1996 Oct 1) Vol. 93, No. 20, pp. 11236-41.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U56976
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19 Dec 1996
Last Updated on STN: 3 Mar 2000
Entered Medline: 25 Nov 1996

AB Cytosolic extracts from a human lymphoblastoid B-cell line, RPMI-8392, established from a patient with acute lymphocytic leukemia, contain two major forms of cyclic nucleotide phosphodiesterase (PDE): Ca2+-calmodulin dependent PDE (PDE1) and cAMP-specific PDE (PDE4). In contrast, normal quiescent human peripheral blood lymphocytes (HPBL) are devoid of PDE1 activity [Epstein, P. M., Moraski, S., Jr., and Hachisu, R. (1987) Biochem. J. 243, 533-539]. Using reverse transcription- polymerase chain reaction (RT-PCR), we show that the mRNA encoding the 63-kDa form of PDE1 (PDE1B1) is expressed in RPMI-8392 cells, but not in normal, resting HPBL. This mRNA is, however, induced in HPBL following mitogenic stimulation by phytohemagglutinin (PHA). Also using RT-PCR, the full open reading frame for human PDE1B1 cDNA was cloned from RPMI-8392 cells and it encodes a protein of 536 amino acids with 96% identity to bovine, rat, and mouse species. RT-PCR also identifies the presence of PDE1B1 in other human lymphoblastoid and leukemic cell lines of B- (RPMI-1788, Daudi) and T-(MOLT-4, NA, Jurkat) cell origin. Inhibition of PDE1 or PDE4 activity by selective inhibitors induced RPMI-8392 cells, as well as the other cell lines, to undergo apoptosis. Culture of RPMI-8392 cells with an 18-bp phosphorothioate antisense oligodeoxynucleotide, targeted against the translation initiation region of the RPMI-8392 mRNA, led to a specific reduction in the amount of PDE1B1 mRNA after 1 day, and its disappearance after 2 days, and induced apoptosis in these cells in a sequence specific manner. This suggests that PDEs, particularly PDE1B1, because its expression is selective, may be useful targets for inducing the death of leukemic cells.

L5 ANSWER 4 OF 7 MEDLINE on STN
ACCESSION NUMBER: 94071102 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 8250251
TITLE: A phosphodiesterase assay using alumina microcolumns.
AUTHOR: Smith B J; Wales M R; Jappy J W; Perry M J
CORPORATE SOURCE: Celltech Limited, Slough, Berkshire, England.
SOURCE: Analytical biochemistry, (1993 Oct) Vol. 214, No. 1, pp. 355-7.
Journal code: 0370535. ISSN: 0003-2697.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199401
ENTRY DATE: Entered STN: 1 Feb 1994
Last Updated on STN: 3 Mar 2000
Entered Medline: 5 Jan 1994

L5 ANSWER 5 OF 7 MEDLINE on STN
ACCESSION NUMBER: 93108304 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1335058
TITLE: Stimulation of beta adrenoceptors in a human monocyte cell line (U937) up-regulates cyclic AMP-specific phosphodiesterase activity.
AUTHOR: Torphy T J; Zhou H L; Cieslinski L B
CORPORATE SOURCE: Department of Inflammation & Respiratory Pharmacology, SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania.
SOURCE: The Journal of pharmacology and experimental therapeutics, (1992 Dec) Vol. 263, No. 3, pp. 1195-205.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199301
ENTRY DATE: Entered STN: 12 Feb 1993
Last Updated on STN: 3 Mar 2000
Entered Medline: 22 Jan 1993

AB Experiments were conducted using undifferentiated U937 cells, a human monocytic cell line, to establish an in vitro model to examine the hormonal regulation of the cyclic AMP (cAMP)-specific phosphodiesterase (PDE IV). Standard chromatographic techniques, coupled with the use of inhibitors and activators that are selective for various phosphodiesterase (PDE) isozymes, were used to establish the PDE isozyme profile in supernatant fractions of U937 cells. When PDE activity was assessed using 1 microM [3H]cAMP as a substrate, 70 to 90% of the total U937 cell supernatant activity in the major peak eluting from anion-exchange columns was inhibited by 30 microM rolipram, a selective inhibitor of PDE IV. The remaining activity was nearly abolished by 10 microM siguazodan or 10 microM cyclic GMP (cGMP,) selective inhibitors of the cGMP-inhibited PDE. Kinetic analyses of the enzyme activity contained within this major peak of PDE activity revealed a cAMP Km = 3 microM and a rolipram Ki = 0.5 microM, values characteristic of PDE IV. Additional studies revealed the presence of a small amount of Ca++/calmodulin-stimulated PDE, but no cGMP-stimulated PDE or cGMP-specific PDE activity. In an effort to induce PDE activity in intact U937 cells by producing a sustained increase in cAMP content, cells were treated for 4 hr with salbutamol (1 microM), rolipram (30 microM) or a combination of both agents. The combination of salbutamol and rolipram produced a 2- to 3-fold increase in PDE activity in U937 cells; when used alone, rolipram was without effect whereas salbutamol induced an increase that was approximately one-half of that observed with the combination. Isozyme isolation and characterization revealed that the overall elevation of

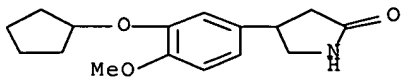
cellular PDE activity could be accounted for by a 2- to 3-fold increase in the Vmax of PDE IV with no change in its Km. The induction of PDE IV by salbutamol was: 1) concentration- and time-dependent; 2) detectable only after prolonged (2-4 hr) agonist exposure; 3) preceded by an increase in cAMP content and an activation of cAMP-dependent protein kinase; 4) mimicked by 8-bromo-cAMP and prostaglandin E2; 5) reversible within 3 hr of salbutamol removal; and 6) abolished by cycloheximide or actinomycin D. Collectively, these results indicate that the major PDE isozyme in the soluble fraction of U937 cells is PDE IV and that the activity of this enzyme is increased markedly in cells after prolonged exposure to agents that increase cAMP content.

L5 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:646421 CAPLUS Full-text
DOCUMENT NUMBER: 130:261
TITLE: Type 4 cyclic adenosine monophosphate phosphodiesterase as a therapeutic target in chronic lymphocytic leukemia
AUTHOR(S): Kim, Doo Ho; Lerner, Adam
CORPORATE SOURCE: Department of Medicine, Section of Hematology and Oncology, Boston Medical Center, Boston, MA, 02118, USA
SOURCE: Blood (1998), 92(7), 2484-2494
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Theophylline, a drug known to inhibit several classes of adenosine 3'5' cyclic monophosphate (cAMP) phosphodiesterases (PDEs), induces apoptosis in chronic lymphocytic leukemia (CLL) cells. Because the PDE target for theophylline in CLL remains unknown, the authors examined the ability of isoform-specific PDE inhibitors to increase cAMP levels and induce apoptosis in primary CLL cells. Reverse transcriptase-polymerase chain reaction of purified CLL cDNA amplified transcripts for PDE1B, 4A and 4B. The type 4 PDe inhibitor rolipram but not the type 1 inhibitor vinpocetine increased CLL cAMP levels. Rolipram-inhibitable (type 4) but not calcium-calmodulin augmented (type 1) PDE enzyme activity was detected in CLL samples. In samples from 13 of 14 CLL patients, rolipram induced apoptosis in a dose-dependent fashion over a 48-h period. Interleukin-2 (IL-2)-cultured whole mononuclear cells (WMC) and anti-Ig stimulated CD19+ B cells were resistant to the induction of apoptosis by rolipram while unstimulated CD19+ B cells, which had a high basal apoptotic rate, were more sensitive. Rolipram stimulated elevations in cAMP levels in all four of these cell populations, suggesting that they differed in sensitivity to cAMP-induced apoptosis. Consistent with this hypothesis, incubation with the cell permeable cAMP analog dibutyryl-cAMP induced apoptosis in CLL cells and unstimulated B cells but not in IL-2-cultured WMC or anti-Ig stimulated B cells. These data identify PDE4 as a family of enzymes whose inhibition induces apoptosis in CLL cells.

IT 61413-54-5, Rolipram
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(4 cyclic adenosine monophosphate phosphodiesterase as a therapeutic target in chronic lymphocytic leukemia)

RN 61413-54-5 CAPLUS
CN 2-Pyrrolidinone, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]- (9CI) (CA INDEX NAME)



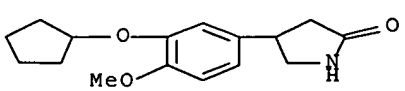
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:414523 CAPLUS Full-text
DOCUMENT NUMBER: 129:130969
TITLE: Cyclic AMP-specific phosphodiesterase inhibitor rolipram and RO-20-1724 promoted apoptosis in HL60 promyelocytic leukemic cells via cyclic AMP-independent mechanism
AUTHOR(S): Zhu, Wen-Hui; Majluf-Cruz, Abraham; Omburo, George A.
CORPORATE SOURCE: The Sol Sherry Thrombosis Research Center, Temple University School of Medicine, Philadelphia, PA, 19140, USA
SOURCE: Life Sciences (1998), 63(4), 265-274
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Phosphodiesterases (PDEs) are responsible for the hydrolysis of cAMP and cGMP which act as intracellular second messengers in a variety of cellular functions. In this paper we report that PDE3 and PDE4 were two dominant classes of PDEs expressed in HL60 cells. The influence of specific PDE inhibitors on apoptosis in HL60 cells was studied. The nonspecific inhibitor IBMX and PDE3-specific inhibitors (milrinone and trequinsin) did not promote apoptosis. They inhibited apoptosis induced by paclitaxel or thapsigargin. However, PDE4-specific inhibitors (rolipram and RO-20-1724) promoted apoptosis within 5 h. In HL60 cells, other cAMP-eliciting reagents (8-bromo-cAMP, Sp-cAMP and forskolin) also inhibited apoptosis, while cell-permeable cGMP analogs did not affect apoptosis. Therefore, IBMX and PDE3-specific inhibitors may prevent HL60 cells from apoptosis by increasing intracellular cAMP. However, apoptosis induced by PDE4-specific inhibitors is not likely due to increased cAMP level. These results suggest that rolipram and RO-20-1724 promoted apoptosis in HL60 cells through cAMP-independent mechanism.

IT 61413-54-5, Rolipram
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rolipram and RO-201724 promote apoptosis in promyelocytic leukemia via cAMP-independent mechanism)

RN 61413-54-5 CAPLUS
CN 2-Pyrrolidinone, 4-[3-(cyclopentyloxy)-4-methoxyphenyl]- (9CI) (CA INDEX NAME)



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REFERENCE COUNT:          23    THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS
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L1             STRUCTURE UPLOADED
L2           1 S L1 EXA

     FILE 'MEDLINE, CAPLUS, WPIDS, USPATFULL' ENTERED AT 10:43:08 ON 25 JAN
     2007
L3        2155 S L2
L4         995 S L3 NOT PY>1998
L5           7 S L4 AND LEUKEMIA
L6       16789 S L4 AND CLL OR "CHRONIC LYMPHOCYTIC LEUKEMIA"
L7           2 S L4 AND (CLL OR "CHRONIC LYMPHOCYTIC LEUKEMIA")

     FILE 'STNGUIDE' ENTERED AT 10:44:52 ON 25 JAN 2007

     FILE 'MEDLINE, CAPLUS' ENTERED AT 10:50:30 ON 25 JAN 2007

     FILE 'STNGUIDE' ENTERED AT 10:50:32 ON 25 JAN 2007

=> s "PDE4" and (CLL or "chronic lymphocytic leukemia")
             0 "PDE4"
             0 CLL
             0 "CHRONIC"
             0 "LYMPHOCYTIC"
             0 "LEUKEMIA"
             0 "CHRONIC LYMPHOCYTIC LEUKEMIA"
                 ("CHRONIC"(W)"LYMPHOCYTIC"(W)"LEUKEMIA")
L8           0 "PDE4" AND (CLL OR "CHRONIC LYMPHOCYTIC LEUKEMIA")

=> s ("type 4 PDE" or "phoshphodiesterase type IV")
           173 "TYPE"
           133 "4"
             0 "PDE"
             0 "TYPE 4 PDE"
                 ("TYPE"(W)"4"(W)"PDE")
             0 "PHOSHPHODIESTERASE"
           173 "TYPE"
             0 "IV"
             0 "PHOSHPHODIESTERASE TYPE IV"
                 ("PHOSHPHODIESTERASE"(W)"TYPE"(W)"IV")
L9           0 ("TYPE 4 PDE" OR "PHOSHPHODIESTERASE TYPE IV")

=> file medline, caplus, wpids, uspatfull
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                               1.02      49.14

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)    SINCE FILE      TOTAL
                                                 ENTRY    SESSION
CA SUBSCRIBER PRICE                               0.00      -2.34

FILE 'MEDLINE' ENTERED AT 11:00:51 ON 25 JAN 2007
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FILE 'CAPLUS' ENTERED AT 11:00:51 ON 25 JAN 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.


FILE 'WPIDS' ENTERED AT 11:00:51 ON 25 JAN 2007


FILE 'USPATFULL' ENTERED AT 11:00:51 ON 25 JAN 2007


=> **s "PDE4" and (CLL or "chronic lymphocytic leukemia")**
L10 151 "PDE4" AND (CLL OR "CHRONIC LYMPHOCYTIC LEUKEMIA")

=> **s l10 not py>1998**
L11 2 L10 NOT PY>1998

=> **d l11 1-2 ibib, abs, hitstr**

L11 ANSWER 1 OF 2 MEDLINE on STN
ACCESSION NUMBER: 1998421394 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9746789
TITLE: Type 4 cyclic adenosine monophosphate phosphodiesterase as a therapeutic target in chronic lymphocytic leukemia.
AUTHOR: Kim D H; Lerner A
CORPORATE SOURCE: Department of Medicine, Section of Hematology and Oncology, Boston Medical Center, Boston, MA 02118, USA.
SOURCE: Blood, (1998 Oct 1) Vol. 92, No. 7, pp. 2484-94.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 29 Oct 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 19 Oct 1998

AB Theophylline, a drug known to inhibit several classes of adenosine 3'5' cyclic monophosphate (cAMP) phosphodiesterases (PDEs), induces apoptosis in chronic lymphocytic leukemia (CLL ) cells. Because the PDE target for theophylline in CLL remains unknown, we examined the ability of isoform-specific PDE inhibitors to increase cAMP levels and induce apoptosis in primary CLL cells. Reverse transcriptase-polymerase chain reaction of purified CLL cDNA amplified transcripts for PDE1B, 4A and 4B. The type 4 PDE inhibitor rolipram but not the type 1 inhibitor vinpocetine increased CLL cAMP levels. Rolipram-inhibitable (type 4) but not calcium-calmodulin augmented (type 1) PDE enzyme activity was detected in CLL samples. In samples from 13 of 14 CLL patients, rolipram induced apoptosis in a dose-dependent fashion over a 48-hour period. Interleukin-2 (IL-2)-cultured whole mononuclear cells (WMC) and anti-Ig stimulated CD19(+) B cells were resistant to the induction of apoptosis by rolipram while unstimulated CD19(+) B cells, which had a high basal apoptotic rate, were more sensitive. Rolipram stimulated elevations in cAMP levels in all four of these cell populations, suggesting that they differed in sensitivity to cAMP-induced apoptosis. Consistent with this hypothesis, incubation with the cell permeable cAMP analog dibutyryl-cAMP induced apoptosis in CLL cells and unstimulated B cells but not in IL-2-cultured WMC or anti-Ig stimulated B cells. These data identify PDE4 as a family of enzymes whose inhibition induces apoptosis in CLL cells.

L11 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:646421 CAPLUS Full-text
DOCUMENT NUMBER: 130:261
TITLE: Type 4 cyclic adenosine monophosphate phosphodiesterase as a therapeutic target in chronic lymphocytic leukemia
AUTHOR(S): Kim, Doo Ho; Lerner, Adam
CORPORATE SOURCE: Department of Medicine, Section of Hematology and Oncology, Boston Medical Center, Boston, MA, 02118, USA
SOURCE: Blood (1998), 92(7), 2484-2494
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Theophylline, a drug known to inhibit several classes of adenosine 3'5' cyclic monophosphate (cAMP) phosphodiesterases (PDEs), induces apoptosis in chronic lymphocytic leukemia (CLL ) cells. Because the PDE target for theophylline in CLL remains unknown, the authors examined the ability of isoform-specific PDE inhibitors to increase cAMP levels and induce apoptosis in primary CLL cells. Reverse transcriptase-polymerase chain reaction of purified CLL cDNA amplified transcripts for PDE1B, 4A and 4B. The type 4 PDe inhibitor rolipram but not the type 1 inhibitor vinpocetine increased CLL cAMP levels. Rolipram-inhibitable (type 4) but not calcium-calmodulin augmented (type 1) PDE enzyme activity was detected in CLL samples. In samples from 13 of 14 CLL patients, rolipram induced apoptosis in a dose-dependent fashion over a 48-h period. Interleukin-2 (IL-2)-cultured whole mononuclear cells (WMC) and anti-Ig stimulated CD19+ B cells were resistant to the induction of apoptosis by rolipram while unstimulated CD19+ B cells, which had a high basal apoptotic rate, were more sensitive. Rolipram stimulated elevations in cAMP levels in all four of these cell populations, suggesting that they differed in sensitivity to cAMP-induced apoptosis. Consistent with this hypothesis, incubation with the cell permeable cAMP analog dibutyryl-cAMP induced apoptosis in CLL cells and unstimulated B cells but not in IL-2-cultured WMC or anti-Ig stimulated B cells. These data identify PDE4 as a family of enzymes whose inhibition induces apoptosis in CLL cells.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> **d his**

(FILE 'HOME' ENTERED AT 10:42:14 ON 25 JAN 2007)

FILE 'REGISTRY' ENTERED AT 10:42:28 ON 25 JAN 2007
L1 STRUCTURE UPLOADED
L2 1 S L1 EXA

FILE 'MEDLINE, CAPLUS, WPIDS, USPATFULL' ENTERED AT 10:43:08 ON 25 JAN 2007
L3 2155 S L2
L4 995 S L3 NOT PY>1998
L5 7 S L4 AND LEUKEMIA
L6 16789 S L4 AND CLL OR "CHRONIC LYMPHOCYTIC LEUKEMIA"
L7 2 S L4 AND (CLL OR "CHRONIC LYMPHOCYTIC LEUKEMIA")

FILE 'STNGUIDE' ENTERED AT 10:44:52 ON 25 JAN 2007

FILE 'MEDLINE, CAPLUS' ENTERED AT 10:50:30 ON 25 JAN 2007

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     FILE 'STNGUIDE' ENTERED AT 10:50:32 ON 25 JAN 2007
L8             0 S "PDE4" AND (CLL OR "CHRONIC LYMPHOCYTIC LEUKEMIA")
L9             0 S ("TYPE 4 PDE" OR "PHOSHPHODIESTERASE TYPE IV")

     FILE 'MEDLINE, CAPLUS, WPIDS, USPATFULL' ENTERED AT 11:00:51 ON 25 JAN
     2007
L10          151 S "PDE4" AND (CLL OR "CHRONIC LYMPHOCYTIC LEUKEMIA")
L11            2 S L10 NOT PY>1998

=> s ("type 4 PDE" or "phoshphodiesterase type IV")
L12           73 ("TYPE 4 PDE" OR "PHOSHPHODIESTERASE TYPE IV")

=> s l12 and leukemia
L13            8 L12 AND LEUKEMIA

=> s l13 not py>1998
L14            2 L13 NOT PY>1998

=> d l14 1-2 ibib, abs

L14  ANSWER 1 OF 2     MEDLINE on STN
ACCESSION NUMBER:    1998421394      MEDLINE  Full-text
DOCUMENT NUMBER:     PubMed ID: 9746789
TITLE:               Type 4 cyclic adenosine monophosphate phosphodiesterase as
                     a therapeutic target in chronic lymphocytic
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AUTHOR:              Kim D H; Lerner A
CORPORATE SOURCE:    Department of Medicine, Section of Hematology and Oncology,
                     Boston Medical Center, Boston, MA 02118, USA.
SOURCE:              Blood, (1998 Oct 1) Vol. 92, No. 7, pp. 2484-94.
                     Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:         199810
ENTRY DATE:          Entered STN: 29 Oct 1998
                     Last Updated on STN: 3 Mar 2000
                     Entered Medline: 19 Oct 1998
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or anti-Ig stimulated B cells. These data identify PDE4 as a family of enzymes whose inhibition induces apoptosis in CLL cells.

L14 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:646421 CAPLUS Full-text
DOCUMENT NUMBER: 130:261
TITLE: Type 4 cyclic adenosine monophosphate phosphodiesterase as a therapeutic target in chronic lymphocytic leukemia
AUTHOR(S): Kim, Doo Ho; Lerner, Adam
CORPORATE SOURCE: Department of Medicine, Section of Hematology and Oncology, Boston Medical Center, Boston, MA, 02118, USA
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FILE 'REGISTRY' ENTERED AT 10:42:28 ON 25 JAN 2007
L1 STRUCTURE UPLOADED
L2 1 S L1 EXA

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L3 2155 S L2
L4 995 S L3 NOT PY>1998
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L6 16789 S L4 AND CLL OR "CHRONIC LYMPHOCYTIC LEUKEMIA"
L7 2 S L4 AND (CLL OR "CHRONIC LYMPHOCYTIC LEUKEMIA")

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     FILE 'MEDLINE, CAPLUS' ENTERED AT 10:50:30 ON 25 JAN 2007

     FILE 'STNGUIDE' ENTERED AT 10:50:32 ON 25 JAN 2007
L8             0 S "PDE4" AND (CLL OR "CHRONIC LYMPHOCYTIC LEUKEMIA")
L9             0 S ("TYPE 4 PDE" OR "PHOSHPHODIESTERASE TYPE IV")

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     2007
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L12           73 S ("TYPE 4 PDE" OR "PHOSHPHODIESTERASE TYPE IV")
L13            8 S L12 AND LEUKEMIA
L14            2 S L13 NOT PY>1998

=>

---Logging off of STN---


=>
Executing the logoff script...


=> LOG Y

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    41.13      90.27

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -1.56      -3.90

STN INTERNATIONAL LOGOFF AT 11:02:47 ON 25 JAN 2007
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